REMARKS

Applicants respectfully request reconsideration of the present application in view of the foregoing amendments and in view of the reasons that follow.

I. Amendments to the specification

The paragraph spanning page 18, line 29 to page 19, line 13, is amended to state that the animals were injected with *Escherichia coli* rather than LPS. This correction is supported by the remainder of the same paragraph, and Experimental Example 3 (pages 100-101), which make clear that mice were injected with *Escherichia coli.*

In the paragraph at lines 3-24 on page 46, each previous recitation of "(compound n)" is amended to "(compound n')." This amendment merely corrects an error in the English translation of the Japanese language specification and is supported by the specification from page 95, line 13 to page 97, line 5, which includes Tables 13 and 14.

The paragraph at lines 4-22 on page 70 is amended to replace "combination drug" with "cycloalkene compound or compound A." Support for this correction can be found within the same paragraph, *e.g.* lines 18 and 19 on page 70. Support can also be found at page 59, lines 4 and 5, of the parent Japanese-language PCT application.

These amendments do no add new matter, and their entry and consideration are respectfully sought.

II. Amendments to the claims

Claims 1-4 and 6 are cancelled, and claims 6-20 are withdrawn.

The subject matter of the cancelled claims is found in amended claim 5 and new claims 21-23. New claims 21 and 22 correspond to cancelled claims 3 and 4. New claim 23 recites a list of compounds within the genus represented by formulas (I) and (II), and is supported by the specification at page 40, lines 5-16, and page 46, lines 22-27. The phrase "severe sepsis" in claim 5 is also amended to recite "severe sepsis associated with organ failure, hypoperfusion, and/or hypotension," which is supported by the specification at page 7, lines 14-16. The phrases "prophylaxis" and "prodrug" are cancelled.

The pending claims are within the scope of the elected claims 1-6, and are therefore properly presented for examination. The foregoing amendments are made solely to advance prosecution and without acquiescing to any rejection, reserving the right to pursue cancelled subject matter in continuing applications with the same rights of priority as the present application.

Following the foregoing amendments, claims 5 and 7-23 are pending, with claims 5 and 21-23 under examination.

III. Rejections under 35 U.S.C. § 112, first paragraph

The Office acknowledges that claims 1-6 are enabled for a method of treatment of severe sepsis, but alleges that they lack enablement for a method of prophylaxis of same. *See* pages 2-5 of the Office Action. Without acquiescing in the grounds of rejection, Applicants have amended the claims to remove recitation of "prophylaxis," solely to advance prosecution. Applicants respectfully request reconsideration and withdrawal of the rejection as it might have been applied to claims 5 and 21-23.

IV. Rejections under 35 U.S.C. § 112, second paragraph

At pages 5-7 of the Office Action, claims 1-6 are rejected as allegedly indefinite for recitation of "prodrug" and, independently, for claim 6's recitation of "use." Applicants respectfully traverse the rejection based on recitation of "prodrug." Solely to advance prosecution, however, the foregoing claim amendments remove the bases of the indefiniteness rejections. Applicants respectfully request reconsideration and withdrawal of the rejection as it might have been applied to claims 5 and 21-23.

V. Rejections under 35 U.S.C. § 101

The rejection of claim 6 for recitation of a "use," at page 7 of the Office Action, is rendered moot by cancellation of claim 6. Applicants respectfully request reconsideration and withdrawal of the rejection.

VI. Rejections under 35 U.S.C. §§ 102(b), 103(a)

Claims 1-3 and 5-6 are alleged to be anticipated by EP 1063228 to Ichimori *et al.* ("Ichimori"), and claim 4 is alleged to be rendered obvious by the combination of Ichimori with U.S. Patent No. 5714469 to DeMarsh *et al.* ("DeMarsh"). As an initial matter, claims 1-4 and 6 are cancelled, rendering moot their rejection. Applicants respectfully traverse the rejection as it might have been applied to pending claims 5 and 21-23.

(a) Ichimori does not disclose or enable the present invention

Ichimori discloses compounds for the treatment of sepsis or septic shock, and discloses that some of the compounds are effective in inhibiting NO and cytokine production from RAW264.7 cells *in vitro* (page 81-84). When compounds 1 or 3 were administered to female BALB/c mice one hour *before* administration of LPS, compounds 1 and 3 inhibited NO production, and compound 1 inhibited cytokine production (pages 84-85). The PCT equivalent of Ichimori is discussed in the present specification from page 2, line 24 to page 7, line 31, noting that:

> However, it has not been suggested if [the compounds of Ichimori] show a treatment effect on sepsis after a considerable time from the onset, particularly, after the onset of severe sepsis associated with organ failure, hypoperfusion, hypotension and the like. Furthermore, a detail of the action mechanism of these compounds has not been clarified.
>
> In recent years, accumulation of information relating to inflammatory mediators, such as NO and cytokine, has been ongoing and the role of complicated networks in the biological phenomena has been elucidated. It has been clarified that various mediators are playing key roles in the response to invasion as well. It has come to be known that inflammatory mediators are also involved in the occurrence of organ failure associated with septic shock and sepsis, which has been conventionally considered to be caused by microorganisms and toxins thereof, and the understanding of sepsis, septic shock and organ failure has been dramatically changing. Sepsis is defined to be a systemic inflammatory response syndrome caused by infectious diseases (Chest, Vol. 101, pages 1644-1655 (1992)), and the essential disease state is considered to be caused by excessive production of inflammatory mediators such

> as NO and cytokine. In fact, there are many reports on the effectiveness of an antiinflammatory mediator therapy on individual inflammatory mediators in initial stages in animal models. In connection with substances that suppress the above-mentioned inflammatory mediators, moreover, many clinical tests targeting sepsis (severe sepsis) patients associated with organ failure, hypoperfusion, hypotension and the like have been ongoing.
>
> As mentioned above, while the effectiveness of a substance that suppresses an inflammatory mediator on sepsis has been shown at an animal model level, clinical tests of an antiinflammatory mediator therapy for severe sepsis patients in US and Europe have not shown any expected effects so far (British Medical Bulletin, Vol. 55, pages 212-225 (1999)). One of the reasons therefor is considered to be the fact that efficacy evaluation in an animal model was performed by administration before the onset of sepsis but, in clinical tests, a drug was administered after the onset of sepsis, particularly, sepsis associated with organ failure, hypoperfusion, hypotension and the like (severe sepsis). It has been also considered difficult for a drug that suppresses each one of complexly intertwined inflammatory mediators to show high effectiveness.

Specification at page 6, line 17 to page 7, line 31 (emphasis supplied). In other words, Ichimori's disclosure that certain compounds inhibit NO or cytokine production does not teach or enable that the same compounds are effective for the treatment of *severe sepsis associated with organ failure, hypoperfusion, and hypotension.* For example, Ichimori demonstrated NO and cytokine inhibition in mice only when compound 1 or 3 was administered one hour before administration of LPS. By comparison, Applicants have demonstrated mouse *survival,* an actual measure of clinical effectiveness, when compounds were administered even *several hours after* a lethal challenge with *E. coli* or LPS. *See* specification at pages 99-102, and Figures 1-5, for example.

The abstract of *British Medical Bulletin*, Vol. 55, pages 212-225 (1999) (available at http://bmb.oxfordjournals.org/cgi/reprint/55/1/212.pdf, accessed November 27, 2009) states that:

> [d]espite intensive efforts, the development of novel drugs for the treatment of sepsis has proved to be extremely difficult. A

> large number of clinical trials have ended in failure. A critical analysis of this record suggests that there is no single reason for these problems. Rather, the explanation lies in part with unexpected failures in the drugs themselves, and in part with the difficulties of trial design in this particular group of patients. In future, trials in this area are likely to be more highly focused, with even stricter protocol definitions to try and ensure a homogeneous patient population

This article demonstrates that the person of ordinary skill in the art recognizes that treatment of some aspects of sepsis has repeatedly failed to demonstrate treatment of severe sepsis, such as is associated with organ failure, hypoperfusion and/or hypotension. Accordingly, the methodological deficiencies of Ichimori prevent the person of ordinary skill from concluding that the compounds of Ichimori are effective in the treatment of severe sepsis.

Thus, Applicants have found the surprisingly beneficial result that these compounds are able to treat severe and lethal sepsis, which, as noted in the *British Medical Bulletin*, Vol. 55, pages 212-225 (1999), is an unmet and long-felt need.

(b) Ichimori does not anticipate

Under 35 U.S.C. § 102, a claim can only be anticipated if every element in the claim is expressly or inherently disclosed in a single prior art reference. *See Kalman v. Kimberly Clark Corp.*, 713 F.2d 760, 771 (Fed. Cir. 1983), *cert. denied*, 465 U.S. 1026 (1984). In addition, a claim can only be anticipated by a publication if the publication describes the claimed invention with sufficient enabling detail to place the public in possession of the invention. *See In re Donohue*, 766 F.2d 531, 533 (Fed. Cir. 1985); *see also PPG Industries, Inc. v. Guardian Industries Corp.*, 75 F.3d 1558, 1566 (Fed. Cir. 1996) ("To anticipate a claim, a reference must disclose every element of the challenged claim and enable one skilled in the art to make the anticipating subject matter").

Ichimori does not anticipate because it does not disclose that the cited compounds are effective for the *treatment of severe sepsis associated with organ failure, hypoperfusion and/or hypotension.* Even if Ichimori did make such a disclosure, it would not anticipate because it does not *enable* the claimed method of treating *severe* sepsis associated with organ failure, hypoperfusion and/or hypotension. Accordingly, Ichimori does not anticipate.

(c) The combination of Ichimori with DeMarsh does not render obvious the claims

DeMarsh is cited for its disclosure of administering ceftazidime for the treatment of sepsis. The disclosure of DeMarsh does not, however, remedy the defects of Ichimori in regard the claims. That is, the combination of Ichimori and DeMarsh does not disclose or enable the claimed method of treatment of severe sepsis associated with organ failure, hypoperfusion and/or hypotension.

Moreover, Applicants' surprising results shown in the specification, and the invention's satisfaction of a long-felt unmet need in relation to *severe* sepsis, are further evidence of the non-obviousness of the claims.

(d) Conclusion

For the above reasons, claims 5 and 21-23 are novel and unobvious. Applicants respectfully request reconsideration and withdrawal of the rejection.

VII. Obviousness-type double patenting rejections

At pages 10-12 of the Office Action, under the doctrine of obviousness-type double patenting (ODP), claims 1-6 are provisionally rejected as obvious variants of claims 14 and 31 of copending Application No. 10/433,826, and claims 1-4 are provisionally rejected over claims 7-8 of copending Application No. 12/226,446. Claims 1-6 are rejected over claims 1-32 of U.S. Patent No. 6,495,604, and claims 1-4 are rejected over claims 1-5 of U.S. Patent No. 7,078,540.

Claims 1-4 are cancelled, rendering moot their rejection or provisional rejection, and overcoming the rejections based on Application No. 12/226,446 and U.S. Patent No. 7,078,540. Applicants respectfully request that the remaining rejections be held in abeyance pending identification of otherwise allowable subject matter.

Nevertheless, as to the potential application of the remaining rejections to pending claims 5 and 21-23, Applicants respectfully traverse. The ODP rejection of the present claims over those of Application No. 12/226,446 is improper in view of the present application's

earlier filing date. The ODP rejection in view of U.S. Patent No. 6,495,60 is believed to be overcome for the same reasons that the claims are not obvious over the prior art. *See* Section VI, above, addressing rejections under 35 U.S.C. § 103. As to Application No. 10/433,826, Applicants note that this rejection is provisional as the claims of both the present and reference rejections are not yet patented.

CONCLUSION

The Examiner is invited to contact the undersigned by telephone if it is felt that a telephone interview would advance the prosecution of the present application.

The Commissioner is hereby authorized to charge any additional fees which may be required regarding this application under 37 C.F.R. §§ 1.16-1.17, or credit any overpayment, to Deposit Account No. 19-0741. Should no proper payment be enclosed herewith, as by the credit card payment instructions in EFS-Web being incorrect or absent, resulting in a rejected or incorrect credit card transaction, the Commissioner is authorized to charge the unpaid amount to Deposit Account No. 19-0741. If any extensions of time are needed for timely acceptance of papers submitted herewith, Applicants hereby petition for such extension under 37 C.F.R. §1.136 and authorize payment of any such extensions fees to Deposit Account No. 19-0741.

Respectfully submitted,

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